REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Interview Summary

Applicant wishes to thank Examiners Canella and Yao for extending the courtesy of discussing this application with Applicant and Applicant's representatives Mary Ann Dillahunty and Ping Hwung, in a personal interview on February 17, 2005. No exhibit was presented. All the pending claims under examination were discussed in view of the references cited in the Office Action. Applicant contended that prior art relevant to this application, such as von Lintig et al. (cited in the Office Action), teaches away from the claimed invention. The Examiners agreed and requested that withdrawn claims be canceled.

As this response is prepared according to these discussions and suggestions, Applicant submits that the currently pending claims are in condition for allowance.

Claim Amendments

Claims 11-50 have been canceled without prejudice or disclaimer as being directed to an unelected invention.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicant submits that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicant reserves the right to file at least one continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Rejection Under 35 U.S.C. §103

A. The rejection of claim 1 under 35 U.S.C. §103 as allegedly unpatentable over Norman et al. (J. Clin. Invest. 105:1035-1038, 2000), in view of Coffey et al. (Science 282:1332-1334, 1998) and Robinson et al. (Curr. Opin. Cell Biol. 9:180-186, 1997) is respectfully traversed for the reasons set forth below.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

The primary reference, Norman et al., was published in April, 2000. However, prior to April, 2000, the claimed invention had been reduced to practice. A Declaration under 37 C.F.R. § 1.131 by the sole inventor of this application, Dr. Matthew C. Coffey, is submitted herewith in support. Therefore, the Norman et al. reference is not prior art with respect to the present application.

Furthermore, in view of the state of the art at the time the priority application was filed, a skilled artisan would not have been motivated to combine Coffey et al. and Robinson et al. and modify the combined teachings to arrive at the present invention. Claim 1 is directed to a method of determining susceptibility of a cell to reovirus infection by measuring constitutive ras-MAP signaling in said cell, wherein the presence of said constitutive signaling indicates susceptibility to infection by reovirus. Coffey et al. teach that reovirus can be used to infect tumors with an activated ras pathway. Robinson et al. teach the MAP kinase is activated by mitogens. Although Coffey et al. disclose that there is a strong correlation between infectibility and high basal level of MAPK activity, and that the latter is a good indication of ras pathway activation, data from

other references available at that time contradict with this notion. For example, von Lintig et al. (Breast Cancer Res. Treatment 62:51-62, 2000), also cited in the Office Action, teach:

> When we measured MAP kinase activity in the cell lines, we found that in serum-starved MCF-7 cells enzyme activity was 0.08pmol/min/mg protein and increased ~3.5-fold with EGF. The basal activity was similar to normal breast tissue and the EGF-stimulated activity was similar to activity in the fibroadenomas and group A cancers. MAP kinase activity in serum-starved MDA-MB-453 cells was 0.25 pmol/mg/min and increased ~1.8-fold with EGF; the EGF-stimulated values are similar to activity in the group B cancers. MAP kinase activity in the MDA-MB-231 cells was high under basal conditions and was not influenced by growth factors. (Page 58, right column, second paragraph of Lintig et al.)

MCF-7, MDA-MB-453, and MDA-MB-231 can all be infected by reovirus. Thus, in two of the three examples of Lintig et al., the MAP kinase was not constitutively activated. These results thus contradict with the role of constitutive MAP kinase activation as an indicator of reovirus susceptibility, and teach away from the present invention.

Other references that teach away from the present invention include Paasinen-Sohns and Holtta[1] (attached herewith as Exhibit A), which teach that cells transformed with the ras oncogene did not show constitutive activation of the MAP kinase (see, e.g., abstract). Similarly, Yip-Schneider et al.[2] (attached herewith as Exhibit B) report that a number of tumor cells with an activating K-ras gene and high levels of Ras-GTP did not display constitutive MAP kinase activation (see, e.g., abstract).

Given the inconsistency in prior art, a skilled artisan would not have been motivated to conclude that constitutive MAP kinase activation is an indicator of reovirus susceptibility. Nor is there a reasonable expectation of using constitutive MAP kinase activation as such an indicator.

---

[1] Paasinen-Sohns A, Holtta E. Cells transformed by ODC, c-Ha-ras and v-src exhibit MAP kinase/Erk-independent constitutive phosphorylation of Sos, Raf and c-Jun activation domain, and reduced PDGF receptor expression. Oncogene. 15(16):1953-66 (1997).

[2] Yip-Schneider MT, Lin A, Barnard D, Sweeney CJ, Marshall MS. Lack of elevated MAP kinase (Erk) activity in pancreatic carcinomas despite oncogenic K-ras expression. Int J Oncol. 15(2):271-9 (1999).

Therefore, the requirement under 35 U.S.C. §103 is not met, and withdrawal of this rejection is respectfully requested.

B. The rejection of claims 1 and 2 under 35 U.S.C. §103 as allegedly unpatentable over Norman et al., Coffey et al., and Robinson et al., and further in view of Current Protocols in Molecular Biology (unit 14.3, printed publication of October, 1998), is respectfully traversed for the same reasons discussed above. Briefly, Norman et al. do not constitute prior art to the present application. The combination of Coffey et al. and Robinson et al. do not render the claimed invention obvious in view of the state of the art. The added reference, Current Protocols in Molecular Biology, teaches methods of measuring ras/MAP activity and does not cure this deficiency. Therefore, withdrawal of this rejection is respectfully requested.

C. Similarly, the rejection of claims 1, 2 and 3 under 35 U.S.C. §103 as allegedly unpatentable over Norman et al., Coffey et al., Robinson et al., Current Protocols in Molecular Biology, and further in view of Wilsbacher et al. (J. Biol. Chem. 272:16988-16994, 1999), is respectfully traversed for the same reasons discussed above. In addition to the previously discussed references, this rejection includes Wilsbacher et al., which teach how phosphorylation of MAP kinase can be measured. Since Wilsbacher et al. does not cure the deficiency of lack of motivation and reasonable expectation of success, the requirement under 35 U.S.C. §103 is also not satisfied by this rejection. Therefore, withdrawal of this rejection is respectfully requested.

D. The rejection of claims 1, 4, and 6-10 under 35 U.S.C. §103 as allegedly unpatentable over von Lintig et al., further in view of Norman et al., Coffey et al., and Robinson et al., is respectfully traversed for the reasons set forth below.

As discussed above, von Lintig et al. contradict with Coffey et al. with respect to the state of MAP kinase activation in reovirus susceptible cells. Therefore, a skilled artisan would not have been motivated to combine these two references and arrive at the claimed invention. The Norman et al. reference is not prior art, and Robinson et al. do not fill in the motivation that is lacking. In any case, the combination of cited references does not provide a reasonable

expectation of success in view of the art that teaches away the present invention (discussed above). Accordingly, withdrawal of this rejection is respectfully requested.

Information Disclosure Statements

Information Disclosure Statements with Forms PTO-1449 were filed in the above-captioned patent application on January 30, 2002, March 13, 2002, and June 21, 2004. Applicants have not yet received the Examiner's copies of the forms PTO-1449, initialed to acknowledge the fact that the Examiner has considered the cited disclosed information.

It is respectfully requested that the Examiner initial and return copies of the subject Forms PTO-1449.

Conclusions

For the reasons set forth above, Applicant submits that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5044.

Enclosed is a $225.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: May 9, 2005

Ping F. Hwung
Reg. No. 44,164

Fish & Richardson P.C.
500 Arguello Street, Suite 500
Redwood City, California 94063
Telephone: (650) 839-5070
Facsimile: (650) 839-5071

50253571.doc